Ankyra Medical Journal

Review DOI: 10.51271/ANKMJ-0016

Approach to restless leg syndrome in hemodialysis patients

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Cite this article: Haktanıyan ZN, Varan E. Approach to restless leg syndrome in hemodialysis patients. *Ank Med J.* 2024;3(3):69-72.

Received: 11.05.2024 ◆ **Accepted**: 17.05.2024 ◆ **Published**: 28.05.2024

ABSTRACT

Restless legs syndrome (RLS) is an uncomfortable urge to move the legs while the person is at rest. This movement disorder is one of the problems that may develop in the follow-up of hemodialysis patients. It is important to recognize and treat these problems because they are closely related to mortality and morbidity. It is estimated that RLS symptoms occur in 3% of the adult population worldwide and in approximately 27% of hemodialysis patients. Although the pathophysiology of the disease and its relationship with its high prevalence in dialysis patients have not yet been clearly elucidated, it is predicted that pathologies such as central dopamine metabolism disorders, iron deficiency and uremia may underlie the disease. There are some pharmacological and non-pharmacological treatment methods developed based on available data. Current data in the literature regarding the effectiveness and superiority of these treatments are insufficient to clarify the treatment approach. Studies on the subject continue and the unknowns in treatment and pathophysiology are being clarified day by day.

Keywords: Restless legs syndrome, Willis-Ekbom disease, hemodialysis

INTRODUCTION

Dialysis patients may face some physical, psychological and social problems due to many reasons such as having a chronic disease, the need for continuous treatment, and the feeling of dependence on treatment. It is predictable that quality of life is lower in these patients compared to the general population.[1] In addition, quality of life in dialysis patients has been found to be closely associated with mortality and morbidity. Because of this close relationship, it is important to recognize and treat problems that may develop during follow-up.[2] Restless leg syndrome (RLS) is one of the conditions that affect the health and quality of life of these patients. RLS also known as Willis-Ekbom disease, is a disturbing urge to move the legs while resting, sitting or sleeping that disrupts sleep.[3,4] Hemodialysis patients constitute a large group of the population likely to be affected by RLS due to severe uremia.[3] RLS symptoms are estimated to occur in 3% of the adult population worldwide.[5] When looking at the prevalence of these symptoms among hemodialysis patients, different prevalence results are found in studies.[6]

Although there are variable results in the literature regarding the prevalence of RLS in hemodialysis patients, it is noteworthy that RLS affects a substantial majority of these patients. Furthermore, studies show that despite its high prevalence, RLS, along with other symptoms that affect patients' lives, is under-recognized and therefore under-treated.[7] The presentation of RLS in these patients is highly variable and symptoms are intermittent and fluctuating, which is predicted to lead to delayed diagnosis.[3] RLS may affect sleep quality and increase the risk of cardiovascular disease in hemodialysis patients.[8] Furthermore, symptom intensity is linked to poor sleep quality, impaired physical functioning and lifestyle standards, and increased mortality risk.[9] Considering all these, it is important to recognize and treat RLS in patients receiving hemodialysis treatment.

DEFINITION

RLS, a neurological sensory-motor disorder that often profoundly affects sleep and quality of life, is often influenced by genetic, environmental and medical factors in the course of the disease. The frequency of symptoms ranges from once a month to every day, and the severity varies considerably from annoying to disabling. The diagnosis of RLS is made by identifying symptom patterns that meet the five basic criteria mentioned in Table 1. Hemodialysis patients are also diagnosed according to these criteria.[10] All five basic criteria must be met for the diagnosis of RLS. In addition to the diagnostic criteria, the International Restless Legs Syndrome Study Group has developed a single standardized question with a sensitivity of 100% and specificity of 96.8% for rapid screening of the disease: 'In the evening or at night when you sleep, do you have unpleasant, restless sensations in your legs? Because of its high sensitivity and specificity, this question can be used for screening purposes in large groups of patients, especially in hemodialysis patients. However,

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the final diagnosis should always be based on diagnostic criteria. In addition, differential diagnoses such as myalgia, leg cramps, arthritis, leg shaking habit, anxiety, myopathy should be kept in mind during the diagnostic phase.[10,11]

Table 1. International Restless Leg Syndrome Study Group diagnostic criteria[10]

The need to move the legs, which is often, but not always, accompanied by or caused by uncomfortable and unpleasant sensations in the legs
These symptoms start or worsen at rest, such as lying or sitting.
These symptoms partially or completely resolve during movement, such as walking or stretching, for as long as the activity continues.
These symptoms occur only in the evening or at night, or are significantly more severe at these times than during the day.
The above symptoms cannot be explained in isolation by symptoms related to another medical or behavioral condition (e.g. leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, foot shaking)

In RLS, it is very important to be able to numerically determine the symptom that bothers the patient the most and the severity of the disease. A number of scales have been developed to objectively measure the patient's level of discomfort and response to treatment. Developed in 2003 by the International RLS Study Group, the disease severity scale is considered the gold standard.

PATHOPHYSIOLOGY AND ETIOLOGY

Although the pathophysiology of RLS is still unknown, iron and dopamine metabolism in the brain are thought to play an important role in the development of the disease.[11] Some genetic variations have also been found to be a risk factor for the development of the disease. When the disease is analyzed etiologically, it is basically divided into primary and secondary. Primary RLS is mostly thought to be due to cerebral iron deficiency, dopamine system dysfunction and increased glutamate levels. Secondary causes include end-stage renal disease, uremia, iron deficiency, drugs and pregnancy.[12]

Pathophysiology and Possible Risk Factors in Hemodialysis Patients

The pathophysiology in hemodialysis patients has not yet been fully elucidated. Since uremia is one of the secondary causes of RLS, it is assumed that RLS is common in end-stage renal disease patients receiving hemodialysis. It is also known that bone-mineral metabolism disorders are encountered in patients with chronic kidney disease. In some studies on the pathophysiology in these patients, hyperphosphatemia was independently associated with the presence of RLS.[13,14] In another study, no significant difference was found between the group with and without RLS symptoms when serum PTH and phosphorus levels were analyzed.[15] Some studies have found that hyperparathyroidism, hyperphosphatemia, and vitamin D deficiency are associated with the incidence and severity of RLS in hemodialysis patients, suggesting that bone metabolism disorder may be associated with RLS.[16]

In terms of the role of genetics in these patients, a study evaluating the association of MEIS1 and BTBD9 polymorphisms with RLS showed significant results in some populations.[17] Another study revealed that hemodialysis patients with RLS symptoms had a significantly longer hemodialysis duration and higher cardiothoracic ratio, as well as higher levels of inflammatory markers and lower transferrin saturations compared to those without RLS symptoms.[18] Uremia-induced pruritus, iron deficiency anemia, and inadequate response to erythropoietin alpha were also found to be associated with RLS in these patients.[3,19] Considering these results, chronic inflammatory process and oxidative stress may also play a role in the development of the disease. In addition, a significant correlation between serum hemoglobin level and the development of RLS has been found in many studies in these patients.[15] It should be kept in mind that anemia, which is frequently encountered in patients with chronic kidney disease, may also be a risk factor for the development of RLS. In terms of iron deficiency, although many studies have found a significant correlation with RLS, the relationship between ferritin and RLS is doubtful since serum ferritin level is an acute phase reactant. When the relationship between serum hepsidin levels and RLS is analyzed, it can be said that significant results were found.[20]

When the relationship between the severity of the disease and some laboratory parameters in hemodialysis patients with RLS symptoms was examined, iron, total iron binding capacity, calcium and transferrin saturation, as well as dialysis duration were found to be associated with the severity of the disease.[21] Among patients receiving hemodialysis, female gender and alcohol use were reported to be risk factors for the development of RLS.[22] Several other studies have also shown that being female was significantly associated with RLS in patients receiving hemodialysis.[23-25] While some studies found a significant relationship between the duration of hemodialysis treatment and RLS.[8,15,26] This relationship was not found in some studies.[23,25] In this group of patients who are likely to encounter psychological problems, there are studies in which anxiety and RLS were found to be related.[13]

Regarding the effect of dialysis modality, it was found that receiving hemodialysis or peritoneal dialysis treatment did not affect the development of RLS or the severity of the disease in patients with RLS.[27]

EPIDEMIOLOGY

When the studies are analyzed, we come across different results regarding the prevalence. Prevalence varies according to several factors such as gender, sample size and geographical region.[6] In 2024, as a result of a meta-analysis evaluating 97 studies conducted in 21 different countries, the global pooled prevalence of RLS in hemodialysis patients was calculated as 27.2%. In the same study, the prevalence was found to be higher in women compared to men.[6]

TREATMENT APPROACHES

Treatment methods can be roughly classified as pharmacologic and non-pharmacologic methods. These treatment approaches are summarized in Table 2. Additional comorbidities in patients should also be considered when evaluating treatment options.[28] Uncertainties in the pathophysiology of the disease do not allow for a clear treatment approach. Moreover, controlled studies on long-term treatment responses and adverse events are limited.[29] As such, the evidence in the literature for the treatment of RLS patients receiving hemodialysis is much more limited. In addition, drugs used in the treatment of primary RLS

may have side effects when used directly in the treatment of RLS patients receiving hemodialysis. According to 2016 guidelines published by the American Academy of Neurology, clinicians are advised to consider prescribing vitamin C and E supplements (Level B evidence) and ropinirole, levodopa or exercise (Level C evidence) for the treatment of RLS in hemodialysis patients. It has been stated that there is insufficient evidence to support or refute the use of gabapentin or IV iron in the treatment of these patients, and insufficient evidence to support or refute the superiority of gabapentin or levodopa over one another.[12]

Table 2. Treatment approaches for RLS in patients receiving hemodialysis treatment

Pharmacological therapies	Non-pharmacological therapies
Dopamine agonists	Cold dialysate
Gabapentins	Massage
Vitamins C and E	Exercise

RLS: Restless legs syndrome

Pharmacological Treatment

Dopamine Agonists: Non-ergot dopamine agonists such as rotigotine, ropinirole and pramipexole are used in the treatment of primary RLS. The number of studies on the use of these drugs in the treatment of hemodialysis-related RLS is limited. In a prospective multicenter study, it was observed that rotigotine improved clinical symptoms of RLS and quality of life in hemodialysis patients.[30] An experiment on mice with rotigotine using serum from dialysis patients suggested that it may be effective in the treatment of RLS in hemodialysis patients.[31] Ropinirole has been shown to improve RLS symptoms, sleep duration and quality of life in dialysis patients and also shows fewer side effects.[32] Pramipexole has a large volume of distribution in the blood and therefore cannot be easily cleared from the blood in hemodialysis patients. In the light of this information, rotigotine or ropirinol may be considered instead of pramipexole as a dopamine agonist in the treatment of hemodialysis patients with RLS. It has been found that dopamine receptor agonists may be associated with various adverse effects such as nausea in the short term and re-exacerbation of symptoms in long-term use.[33,34] Short-term side effects disappear after the drug is discontinued. Due to these side effects that may occur during pharmacologic treatment, non-pharmacologic treatments play an important role in the management of the disease. Due to the potential effect of central dopamine metabolism disorders in the pathophysiology, dopamine receptor agonists may be effective in the treatment of the disease through this pathway.

Gabapentins: The other group of pharmacologic agents used in the treatment of RLS are gabapentins. There is insufficient evidence to support or refute the use of gabapentin in the treatment of dialysis-induced RLS.[12] A meta-analysis in 2022 concluded that gabapentins are the most potent pharmacological agent in the treatment of RLS due to hemodialysis.[35]

Vitamin C and E: According to the American Academy of Neurology guidelines, the first choice pharmacologic agent recommended in patients with RLS secondary to hemodialysis is vitamins C and E.[12] Supplementation of these vitamins can be given singly or in combination. Following these recommendations, a meta-analysis conducted in 2021 concluded that vitamin C, followed by ropirinol, may be the most effective treatment in these patients in the light of available evidence.[35] Considering the antioxidant effects of these vitamins, vitamin E and C can be considered as a safe choice among pharmacological agents in people with RLS symptoms due to hemodialysis. In addition, depression and RLS are closely associated with insomnia in these patients. In addition to treatments for RLS, treatment of depression and insomnia may be useful in improving quality of life in hemodialysis patients.[36]

Non-pharmacological Methods

Cold dialysate: Dialysate is the solution used to stabilize the blood levels of patients receiving hemodialysis. The dialysate temperature is traditionally set at 37°C to maintain isothermia (between 36.5°C-36.9°C). Cold dialysis is performed by lowering the dialysate temperature to 35°C-36°C or 0.5°C below the resting body core temperature. Cold dialysate has the advantage of being one of the easily modifiable treatment options for patients with RLS on hemodialysis, as well as reducing the risk of intradialytic hypotension.[37] In 2022, dopamine agonist, gabapentin, iron, vitamin C, vitamin E, cold dialysate, intradialytic stretching exercise, intradialytic aerobic exercise, intradialytic aerobic exercise and dopamine agonist, aromatherapy massage, reflexology, acupuncture treatment, As a result of a meta-analysis in which 24 studies were evaluated to compare the effectiveness between neuromuscular electrical stimulation treatments, it was concluded that cold dialysate was the most effective treatment in reducing the severity of RLS and gabapentin was the most powerful pharmacological treatment. It has been suggested that there is limited evidence on the effectiveness of massage therapy, which can be considered among other treatment modalities.[35]

Massage: A meta-analysis conducted in 2022 showed that massage therapy reduced the symptoms and severity of RLS due to hemodialysis.[34] In addition, in this study, the effect of massage therapy with lavender oil was examined and it was concluded that lavender oil may also be effective in the treatment of RLS due to its effect on relieving muscle pain and strengthening immunity. The minimal side effect profile is also an advantage of this treatment option. Some studies have suggested that massage therapy has the potential to stimulate the nervous system by accelerating dopamine secretion and thus may be effective in the treatment of RLS.[38]

Exercise: Exercise is one of the non-pharmacologic treatment options in hemodialysis patients. Aerobic exercise or intradialytic stretching exercises have been shown to alleviate pain and improve sleep quality in RLS. In one study, a 6-month exercise training regimen was found to be as effective as 6-month low-dose dopamine agonist treatment in reducing RLS symptoms and improving depression score in uremic patients.[39]

CONCLUSION

Patients receiving hemodialysis treatment face various problems during the disease process. One of these problems is RLS. Despite its high prevalence, RLS in hemodialysis patients is recognized late and therefore treated late in clinical practice. There are pharmacologic and non-pharmacologic treatment approaches for RLS in dialysis patients. Although there are studies on this subject in the literature, the available

data do not allow an optimal approach and treatment route to be established. There is a need for more studies in this patient group in terms of approach to RLS and development of effective treatment methods.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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